APPENDIX A

CM DEXTRAN ABSTRACTS (7)

1: Cancer Biochem Biophys. 1986 Oct;8(4):277-87. Related Articles, Links

Cis-platinum(II) complexes of carboxymethyl-dextran as potential antitumor agents. I. Preparation and characterization.

Schechter B, Pauzner R, Arnon R, Wilchek M.

Cis-diamminedichloro platinum (II) (cis-DDP) and cis-diamminediaquo platinum (II) nitrate (cis-aq) were demonstrated to form complexes with dextran (dex) substituted with carboxymethyl (CM) groups at an average substitution ratio of 1 mole CM per 2 mole glucose units of dextran. The complexes were formed by reacting each of the two platinum (II) derivatives with carboxymethyl-dextran (CM-dex) at room temperature (RT) or at 37 degrees C in an aqueous solution. The complexing rate depended on temperature, ratio of platinum (II) compounds to CM-dex in the reaction mixture, and time of reaction. Experiments were performed with two CM-dex preparations, derived from dex T-10 (Mr-10,000) and from dex T-40 (Mr-40,000). Soluble cis-DDP and cis-aq complexes formed with CM-dex T-10 and CM-dex T-40 could carry up to 15 mole or 60 mole of the platinum (II) compounds per 1 mole CM-dex, respectively but higher complexing ratios resulted in complex precipitation. Reactivity of cis-aq with CM-dex was higher than that of cis-DDP. NaCl interfered with complex formation, but did not cause dissociation of already formed complexes. The binding of cis-DDP and cis-aq to CM-dex is, however, reversible since the drugs could be exchanged by other acceptors of higher affinity to platinum (II) such as O-phyenlenediamine, or DNA.

PMID: 2433021 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother. 1987;25(3):225-30. Related Articles, Links

Selective cytotoxicity against tumor cells by cisplatin complexed to antitumor antibodies via carboxymethyl dextran.

Schechter B, Pauzner R, Arnon R, Haimovich J, Wilchek M.

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Cis-diamminedichloroplatinum (II) (cis-DDP) and its structural analogue cis-diamminediaquoplatinum(II) nitrate (cis-aq) were complexed via an intermediate dextran carrier to antibodies specifically reactive with B lymphoma cells (38C-13). The potential use of these drugs in site-directed immunotargeting was evaluated. The two platinum(II) compounds were previously shown to form pharmacologically active complexes with carboxymethyl dextran (CM-dex). For the purpose of preparing drug-antibody complexes, CM-dex was first conjugated to idiotypic antibodies that recognize a specific membrane IgM on the B lymphoma cells. The conjugates were prepared by a modified water-soluble carbodiimide method in which N-hydroxysuccinimide was used to enhance the coupling reaction. The conjugation was followed by separation of the CM-dex-IgG conjugates from unconjugated CM-dex or IgG. The platinum(II) compounds were then complexed to the CM-dex-IgG resulting in complexes carrying up to 50 mole drug/mole IgG. Both cis-DDP and cis-aq complexes of CM-dex-antibody conjugates maintained most of the original cell-binding activity of the antibodies. An in vitro assay was used to demonstrate selective binding to tumor cells in which the target cells were treated with specific immune complexes and washed before culture. In this assay the specific complexes showed preferential cytotoxicity for the B lymphoma cells in comparison to the free drugs, drug CM-dex, or nonspecific immune complexes.

PMID: 2445485 [PubMed - indexed for MEDLINE]

1: Anal Biochem. 1988 Jan;168(1):25-30. Related Articles, Links

Purification of Escherichia coli alkaline phosphatase on an ion-exchange high-performance liquid chromatographic column using carboxymethyl dextrans.

Dunn BE, Edberg SC, Torres AR.

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Carboxymethyl dextrans (CM-Ds) were used on an HPLC ion-exchange column to obtain significantly enriched alkaline phosphatase (EC 3.1.3.1) from a sample of Escherichia coli periplasmic space proteins without significant loss of enzymatic activity. The ability of CM-Ds to separate alkaline phosphatase even when the column was 80-85% saturated with protein demonstrates the potential for high column capacity using CM-Ds. In addition, the fractions containing alkaline phosphatase and CM-Ds were reapplied to the same ion-exchange column under different buffer conditions and purified to homogeneity by salt gradient elution chromatography, thus demonstrating the compatibility of CM-Ds with the latter chromatographic method. The two-step chromatographic procedure yielded enzyme of purity comparable to that of electrophoretically purified E. coli alkaline phosphatase obtained commercially. These studies demonstrate that HPLC displacement chromatography is a mild procedure which allows rapid, quantitative purification of an enzyme. Scaling up with larger columns should allow purification of enzymes of a commercial basis.

PMID: 2452588 [PubMed - indexed for MEDLINE]

1: Cancer Chemother Pharmacol. 1989;24(3):161-6. Related Articles, Links

Blood levels and serum protein binding of cis-platinum(II) complexed to carboxymethyl-dextran.

Schechter B, Rosing MA, Wilchek M, Arnon R.

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Plasma levels and serum protein binding of cis-diamminedichloroplatinum(II) (cis-DDP) or cis-diammine diaquoplatinum(II) (cis-aq) complexed to carboxymethyl-dextran (CM-dex) with a molecular weight of 10,000 (T-10), 40,000 (T-40), and 250,000 (T-250) were investigated in BALB/c mice. Levels of active drug in the circulation after the i.v. or i.p. administration of the free or complexed drugs, as well as the loss of drug activity due to serum protein binding following incubation with mouse serum, were monitored by an antitumor in vitro assay using a drug-sensitive tumor cell line. Following i.v. injection of the complexes, active platinum(II) was maintained in the circulation at higher levels and for a longer period, whereas the free drug disappeared rapidly. The rate of disappearance of the complexed drug from the circulation was markedly influenced by the molecular size of the carrier CM-dex, since the retained amount of drug was considerably higher with the T-40 and T-250 complexes than with the T-10 complex. An i.p. injection resulted in a rapid and transient appearance of low levels of the free drugs in the blood, whereas in the case of the complexes, transport to the circulation was slower and their maintenance in the blood system was markedly higher. Serum protein binding was much slower with CM-dex-complexed drugs (regardless of the molecular size of the CM-dex carrier) than with the free drugs.

PMID: 2472228 [PubMed - indexed for MEDLINE]

1: Biol Pharm Bull. 1993 Feb;16(2):158-62. Related Articles, Links

Disposition characteristics of model macromolecules in the perfused rat kidney.

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The disposition characteristics of model macromolecules such as dextran (70 kDa), bovine serum albumin (BSA), and their charged derivatives were studied in the perfused rat kidney. In a single-pass indicator dilution experiment, venous and urinary recovery patterns and tissue accumulation of radiolabeled compounds were evaluated under filtering or nonfiltering conditions. In the filtering kidney, cationic macromolecules such as diethylaminoethyl-dextran (DEAE-dex) and cationized BSA (cBSA) accumulated in the kidney to a great extent whereas anionic and neutral macromolecules such as BSA, carboxymethyl-dextran (CM-dex), and dextran showed only small uptake. DEAE-dex and cBSA were distributed to both the medulla and cortex regions of the kidney and their recoveries in the kidney decreased as the injected dose increased. Similar tissue uptake was observed in the nonfiltering kidney perfusion system suggesting that they were mainly taken up by the kidney from the renal capillary side based on electrostatic interaction. In addition, the steady-state distribution volumes of cationic macromolecules calculated from venous outflow patterns were larger than those of the intravascular volume estimated from the distribution volumes of neutral and anionic macromolecules, suggesting their reversible interaction with the vascular wall. On the other hand, dextran derivatives with molecular weight distribution were excreted into urine based on glomerular permselectivity; i.e., cationic DEAE-dex and anionic CM-dex showed enhanced and restricted urinary excretion, respectively, compared with neutral dextran. In contrast, no significant excretion was observed for BSA and cBSA. The utility of the isolated rat kidney perfusion experiment for studying the renal disposition of macromolecular drugs was thus demonstrated.

PMID: 7689886 [PubMed - indexed for MEDLINE]

1: Biol Pharm Bull. 2002 May;25(5):632-41.

J-STAGE

Paclitaxel delivery systems: the use of amino acid linkers in the conjugation of paclitaxel with carboxymethyldextran to create prodrugs.

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Paclitaxel was bound via its hydroxyl group to carboxymethyldextran (CMDex, 150 kDa) by means of an amino acid linker; the linker was introduced into the 2'- or 7-hydroxyl group of the paclitaxel through an ester bond. These conjugates--CMDex-2'-paclitaxel and CMDex-7-paclitaxel--were designed to be water-soluble with a paclitaxel content between 6-8% (w/w) with a degree of subsititution (DS) of the CM groups at 0.6 per sugar residue. The release of the paclitaxel from the conjugates was influenced by the hydroxyl group (2'- or 7-) of paclitaxel to which the amino acid linker was introduced, and by what amino acid was used as the linker. In mouse plasma incubated at 37 degrees C for 72 h, the most paclitaxel was released using CMDex-paclitaxel conjugate with 2'gly followed by, in descending order, 2'-ala, 2'-leu, 2'-ile, and 7-gly as the amino linkers. Colon 26, a Taxol resistant cancer, was introduced into mice and the conjugates were intravenously administered by bolus injection for a tumor distribution study, and intermittently intravenously administered for a tumor growth regression study. In both studies the highest amount of paclitaxel release was found in the CMDex-2'-gly-paclitaxel followed by CMDex-2'-ala-paclitaxel, CMDex-2'-leu-paclitaxel and paclitaxel. There was a direct correlation between the amount of paclitaxel released and the observed efficacy. CMDex-2'-ile-paclitaxel and CMDex-7-gly-paclitaxel did not show any anti-tumor activity. These results clearly demonstrate that a CMDex-paclitaxel with an appropriate amino acid linker has significant anti-tumor activity against colon 26, and that these anti-tumor effects appear to correlate with the amounts of paclitaxel released in the tumor.

PMID: 12033505 [PubMed - indexed for MEDLINE]

1: Biomaterials. 2005 Aug;26(22):4677-83. Epub 2005 Jan 19.

ELSEVIER FULL-TEXT ARTICLE

A novel pH- and ionic-strength-sensitive carboxy methyl dextran hydrogel.

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A fast and simple method for the preparation of pH-sensitive hydrogel membranes for drug delivery and tissue engineering applications has been developed using carbodiimide chemistry. The hydrogels were formed by the intermolecular cross-linking of carboxymethyl dextran (CM-dextran) using 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS). Infrared spectra of the hydrogels suggest the formation of ester bonds between the hydroxyl and carboxyl groups in the CM-dextran. The porosity of the hydrogels produced, as shown by protein diffusion, increases in response to changes in the pH and the ionic strength of the external medium. The results show pH-dependent swelling behaviour arising from the acidic pedant groups in the polymer network. The diffusion of the protein lysozyme through the hydrogel membranes increased with increases in both pH (5.0-9.0) and ionic strength. The effect of changes of pH and ionic strength on the hydrogel's permeability was shown to be reversible. Scanning electron microscopy of these hydrogels showed that pH-dependent changes in permeability are mirrored by morphological changes in gel structure.

PMID: 15722138 [PubMed - indexed for MEDLINE]